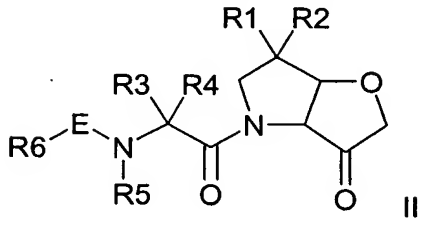
Claims

A compound of the formula II



II

wherein

one of R^1 and R^2 is halo and the other is H or halo;

R^3 is C_1-C_5 straight or branched chain, optionally fluorinated, alkyl;

R^4 is H; or

R^3 together with R^4 defines

a spiro-C_5-C_7 cycloalkyl, optionally substituted with 1 to 3 substituents selected from halo, hydroxyl, C_1-C_4 alkyl or C_1-C_4 haloalkyl; or optionally bridged with a methylene group; or

a C_4-C_6 saturated heterocycle having a hetero atom selected from

O, NRa, S, $S(=O)_2$;

R^5 is independently selected from H or methyl;

E is -C(=O)-, $-S(=O)_m$-, $-NR^5S(=O)_m$-, $-NR^5C(=O)$-, -OC(=O)-,

R^6 is a stable, optionally substituted, monocyclic or bicyclic, carbocycle or hetorocycle wherein the or each ring has 4, 5 or 6 ring atoms and 0 to 3 hetero atoms selected from S, O and N and wherein the optional substituents comprise 1 to 3 members selected from R_7;

R_7 is independently selected from halo, oxo, nitrile, nitro, C_1-C_4 alkyl, -XNRaRb, -$XNRbR^9$, $-NRbC_1$-C_4alkylR^9, NH_2CO-, X-R^9, X-O-R^9, O-X-R^9, X-$C(=O)R^9$, X-$(C=O)NRaR^9$, X-$NRbC(=O)R^9$, X-$NHSO_mR^9$, X-$S(=O)_mR^9$, X-$C(=O)OR^9$, X-$NRbC(=O)OR^9$;

R_9 is independently H, C_1-C_4 alkyl, C_3-C_6 cycloalkyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, thiopyranyl, furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, phenyl, any of which is optionally substituted with R^{10};

R_{10} is independently selected from hydroxy, XR^9, -XNRaRb, $-XNRbR^9$, $-NRbC_1$-C_4alkylR^9, nitro, cyano, carboxy, oxo, C_1-C_4 alkyl, C_1-C_4-alkoxy, C_1-C_4 alkanoyl, carbamoyl;

X is independently a bond or C_1-C_4 alkyl;

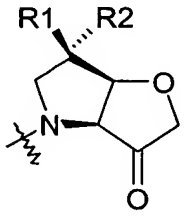
Ra is independently H, C_1-C_4 alkyl or $CH_3C(=O)$;

Rb is independently H, or C_1-C_4 alkyl

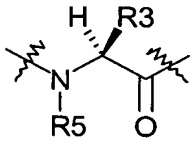
m is independently 0,1 or 2;

or a pharmaceutically acceptable salt or prodrug thereof.

2. A compound according to claim 1, wherein the stereochemistry is as depicted in the partial structure below:



3. A compound according to claim 1, wherein the stereochemistry is as depicted in the partial structure below:



4. A compound according to claim 1, wherein R^2 is halo and R^1 is H.

5. A compound according to claim 4, wherein R^2 is fluoro.

6. A compound according to claim 1, wherein R^1 and R^2 are fluoro.

7. A compound according to claim 1, wherein R^3 is C_1-C_4 branched chain alkyl.

8. A compound according to claim 7, wherein R^3 is iso-butyl.

9. A compound according to claim 1, wherein R^3 and R^4 together define spirocycloalkyl.

10. A compound according to claim 9, wherein R^3 and R^4 together define spirocyclohexyl.

11. A compound according to claim 1, wherein R^5 is H.

12. A compound according to claim 1, wherein E is -C(=O)-.

13. A compound according to claim 1, wherein R^6 is substituted phenyl.

14. A compound according to claim 13, wherein the substituent comprises -NRaRb, -CH_2NRaRb, -NRbR^9, -NRbC_1-C_4alkylR^9, C_1-C_4 straight or branched alkyl or -O-R^9.

15. A compound according to claim 14, wherein the substituent comprises -NH-CH_2phenyl, -NHCH_2pyridyl or -NH-phenyl, wherein each phenyl or pyridyl ring is substituted with C_1-C_4-alkyl, -NRaRb, -NRbR^9 or -NRbC_1-C_4alkylR^9.

16. A compound according to claim 13, wherein the substituent comprises C_3-C_6 cycloalkyl, pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, indolinyl, pyranyl, thiopyranyl, furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, phenyl, any of which is optionally substituted with R^{10}.

17. A compound according to claim 16, wherein the substituent is selected from indolinyl, pyranyl, thiopyranyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, indolyl, any of which is optionally substituted with R^{10}.

18. A compound according to claim 17, wherein the substituent is thiazolyl, 5-methyl-thiazolyl or thienyl, optionally substituted with R^{10}.

19. A compound according to claim 18, wherein the substituent is thiazol-4-yl, 5-methylthiazol-4-yl or thien-2-yl, optionally substituted with R^{10}.

20. A compound according to claim 18, wherein the thiazolyl, 5-methylthiazolyl or theinyl is substituted with morpholinyl, morpholinylmethyl-, piperidinyl, piperidinylmethyl-, piperazinyl, piperazinylmethyl, any of which is substituted with C_1-C_3 alkyl, fluoro, difluoro or C_1-C_3 alkyl-O-C_1-C_3alkyl-.

21. A compound according to claim 20, wherein the substituent to the thiazolyl, 5-methylthiazolyl or thienyl is piperid-4-yl which is substituted with methyl, piperazinyl which is N-substituted with C_1-C_3 alkyl or methyloxyethyl-, -or piperid-1-ylmethyl- which is unsubstituted or 4-substituted with fluoro or di-fluoro.

22. A compound according to claim 13, wherein the substituent comprises a morpholine, piperidine or piperazine ring, optionally substituted with R^{10}.

23. A compound according to claim 22 comprising piperid-4-yl or N-piperazinyl, N-substituted with Ra or piperidin-1-yl which is 4-substituted with -NRaRb.

24. A compound according to claim 1, wherein R^6 is optionally substituted: benzothiazol or benzofuryl or benzoxazolyl.

25. A compound according to claim 24, wherein the substituent is -OR^9, -OXR^9 , -$NRbR^9$ or -$NRbXR^9$.

26. A compound according to claim 25, wherein R^9 is piperid-4-yl, piperazin-1-yl or piperidin-1-yl or morpholino, any of which is substituted with C_1-C_3 alkyl.

27. A compound according to claim 26, wherein the optional substituent to R^6 is N-morpholinylethyloxy, N-methylpiperid-4-yloxy, or N-methylmorpholin-3-ylmethyloxy.

28. A pharmaceutical composition comprising a compound as defined in any of claims 1 to 27 and a pharmaceutically acceptable carrier or diluent therefor.

29 Use of a compound as defined in any of claims 1-27 in the manufacture of a medicament for the treatment of disorders mediated by cathepsin K.

30 Use according to claim 29, wherein the disorder is selected from:
osteoporosis,
gingival diseases such as gingivitis and periodontitis,
Paget's disease,
hypercalcaemia of malignancy
metabolic bone disease
diseases characterised by excessive cartilege or matrix degradation, such as osteoarthritis and rheumatoid arthritis.
bone cancers including neoplasia,
pain.